CLAIMS

1. Compounds of general formula (E) below :

$B_x - L_z - (HR\ Ch)_y$ (E)

in which :

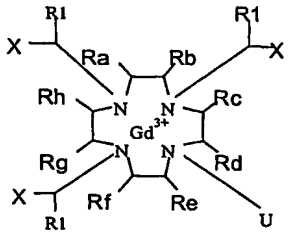
- B is a biovector
- L is a linker
- HR Ch represents a chelate of formula (I) :

$$[\ (D)_q - (I_{a,b,c,d,e,f,g})_r\ ];$$

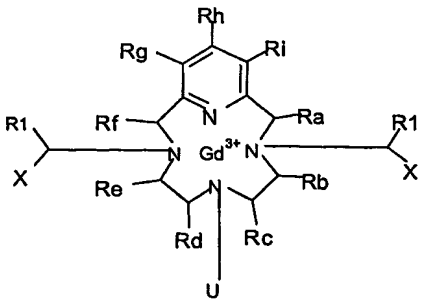
with :

a) $I_{a,b,c,d,e,f,g}$ chosen from I_a , I_b , I_c , I_d , I_e , I_f , I_g,

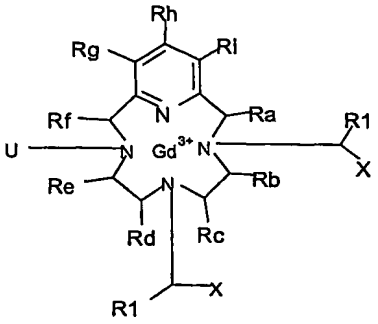
I_a , I_b , I_c having the meanings :



Ia



Ib



Ic

where :

- the X, which may be identical or different, are chosen from $CO_2R'_a$, $CONR'_bR'_c$ or $P(R'_d)O_2H$, with :
  - R'_a, R'_b and R'_c, which may be identical or different, representing H or (C_1-C_8) alkyl, which is optionally hydroxylated ;
  - P is the phosphorus atom, R'_d is chosen from OH, (C_1-C_8)alkyl or (C_1-C_8)alkoxy, (C_1-C_8)arylalkyl or (C_1-C_8)alkoxyalkyl ;

- R1 represents a hydrophilic group of molecular weight greater than 200, selected from groups :

  -polyoxy(C_2-C_3)alkylene, in particular polyethylene glycol and its C_1-C_3 monoethers and monoesters, preferably of molecular mass from 1000 to 2000

  - polyhydroxyalkyl

  - polyol

  - $(R_2g)_e[(R_2g)_iR_3]_h$ where:

    - h = 1 or 2 ; i = 0, 1 or 2 ; e = 1 to 5

    - R_2 represents (the R_2 being identical or different) :

      - nothing, an alkylene, an alkoxyalkylene, a polyalkoxyalkylene;

      - a phenylene, or a heterocyclic residue which may be saturated or unsaturated, optionally substituted with OH, Cl, Br, I, (C_1-C_8)alkyl, (C_1-C_8)alkyloxy, NO2, NR_XR_Y, NR_XCOR_Y, $CONR_XR_Y$ or $COOR_X$, R_X and R_Y being H or (C_1-C_8)alkyl, and the linear, branched or cyclic C_1-C_{14} alkyl, alkylene and alkoxy groups possibly being hydroxylated ;

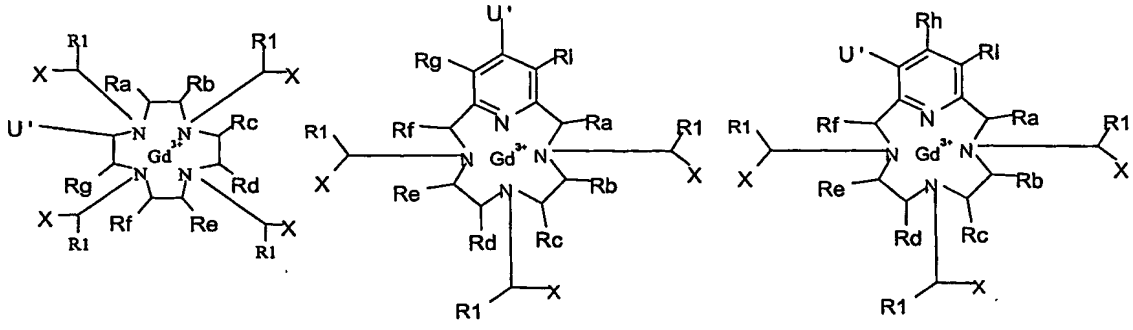
    - g represents (the g being identical or different): nothing or a function O, CO, OCO, COO, SO3, OSO2, CONR', NR'CO, NR'COO, OCONR',NR', NR'CS, CSNR', SO2NR', NR'SO2, NR'CSO, OCSNR',NR'CSNR', P(O)(OH)NR', NR'P(O)-(OH), in which R' is H, (C_1-C_8)alkyl or R_3 ;

    - R_3 represents alkyl, phenyl, alkyl substituted or interrupted with one or more phenyl groups, alkyleneoxy groups; amino or amido unsubstituted or substituted with alkyl optionally substituted or interrupted with one of the above groups; phenyl, phenylene and heterocyclic groups which may be substituted with OH, Cl, Br, I,

(C_1-C_8)alkyl, (C_1-C_8)alkyloxy, NO2, NR_XR_Y, NR_XCOR_Y, $CONR_XR_Y$ or $COOR_X$, R_X and R_Y being H or (C_1-C_8)alkyl, and linear, branched or cyclic C_1-C_{14} alkyl, alkylene and alkoxy groups which may be hydroxylated;

- R_a to R_i independently represent H, alkyl, hydroxyalkyl, alkylphenyl or cycloalkyl.
- U is a group -CXR_4-linker 1, CHR_4CON-linker 1, CHR_4-CHR_5OH-linker 1
- R_4 and R_5 independently representing H, alkyl or hydroxyalkyl,
- X having the meaning above,
- linker 1 being the linker providing the link between a chelate $I_{a, b, c}$, and the linker L when q=0 and between $I_{a, b, c}$, and D when q=1

I_d, I_e, I_f having the meanings :



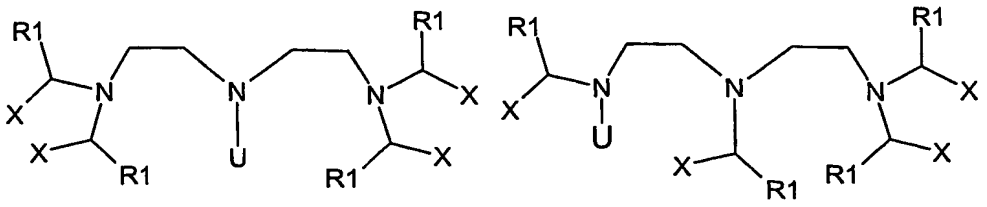
Id

Ie

If

- X, R1, Ra to Ri having the same meaning as above,
- U' is linker 1, providing the link between a chelate $I_{d,e,f}$ and a linker L when q=0 and between $I_{d,e,f}$ and D when q=1,

- I_g representing



U, X, R1 having the same meaning as above, linker 1 providing the link between a chelate I_g and a linker L when q=0 and between I_g and D when q=1.

b)

- q = 0 or q=1
- r=1 when q=0, or r is between 2 and 5 when q=1

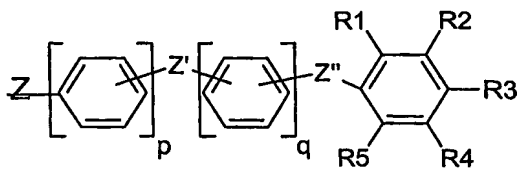
c) D is a polyfunctional molecule capable of linking a linker L to at least two chelates $I_{a,b,c,d,e,f,g}$

d) x, y and z are between 1 and 8, preferably x=1 to 3, y=1 to 6, z=1 to 3, given that y=z ;

and also the salts of the compounds of formula (E) with pharmaceutically acceptable inorganic or organic acids or bases.

2. Compound according to Claim 1, characterized in that R1 is $(CH_2)_xCONHR$ with x=1, 2 or 3 and R is a hydrophilic group of molecular weight greater than 200, chosen from :

1) a group:



IV1

and Z is a bond, CH_2, CH_2CONH or $(CH_2)_2NHCO$

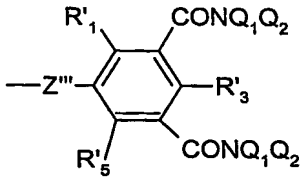
Z' is a bond, O, S, NQ, CH_2, CO, CONQ, NQCO, NQ-CONQ or $CONQCH_2CONQ$,

Z" is a bond, CONQ, NQCO or $CONQCH_2CONQ$

p and q are integers, the sum of which is 0 to 3 ;

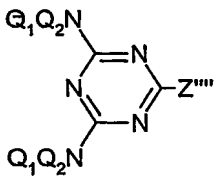
R_1, R_2, R_3, R_4 or R_5 represent:

- either, independently of one another, H, Br, Cl, I, $CONQ_1Q_2$ or NQ_1COQ_2 with Q_1 and Q_2, which may be identical or different, being H or a $(C_1$-$C_8)$alkyl group which is mono- or polyhydroxylated or optionally interrupted with one or more oxygen atoms, and at least one and no more than two of R_1 to R_5 are $CONQ_1Q_2$ or NQ_1COQ_2 ;
- or R_2 and R_4 represent



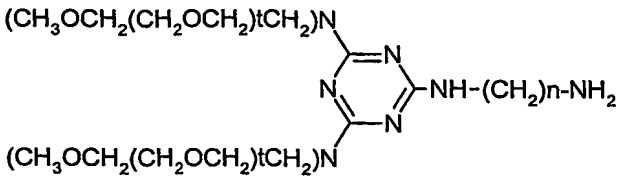
and R_1, R'_1, R_3, R'_3, R_5 and R'_5, which may be identical or different, represent H, Br, Cl or I, Q_1 and Q_2 have the same meaning as above and Z''' is a group chosen from CONQ, $CONQCH_2CONQ$, $CONQCH_2$, NQCONQ and $CONQ(CH_2)_2NQCO$ and Q is H or $(C_1$-$C_4)$alkyl, which is optionally hydroxylated, it being possible for the alkyl groups to be linear or branched ;

2) a "flash" branch

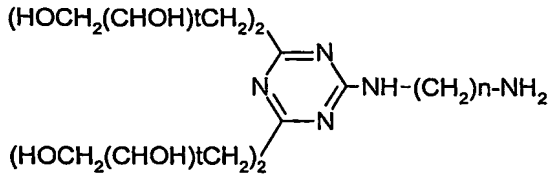


with Z'''' being $NQ(CH_2)_j(CH_2OCH_2)_i(CH_2)_jNH_2$ with i = 2 to 6 and j = 1 to 6,

preferably



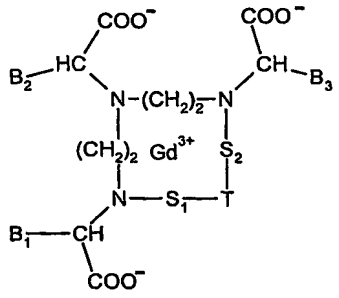
or



with t =1, 2, 3 or 4 and n=2 to 6.

3. Compound according to Claim 1 or 2, characterized in that q=1.

4. Compound according to Claim 1 or 2, characterized in that HR Ch represents the group :

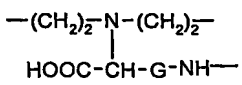


II 1

in which :

$-S_1-T-S_2-$ is

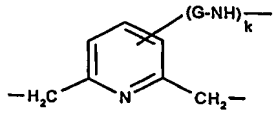
1) either



where $S_1 = S_2 = (CH_2)_2$

with all three of B_1, B_2 and B_3 representing $(CH_2)_xCONHR$ with x = 1, 2 or 3

2) or

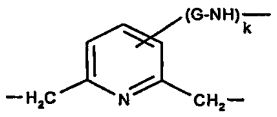


III_1

with k = 0 and $S_1 = S_2 = CH_2$

one of B1, B2, B3 representing G-NH, and the others representing $(CH_2)_xCONHR$

3) or



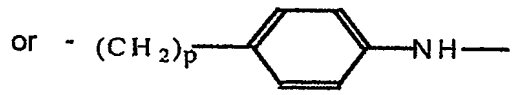
III_1

with k=1

all three of B_1, B_2, B_3 representing $(CH_2)_xCONHR$ with x = 1, 2 or 3

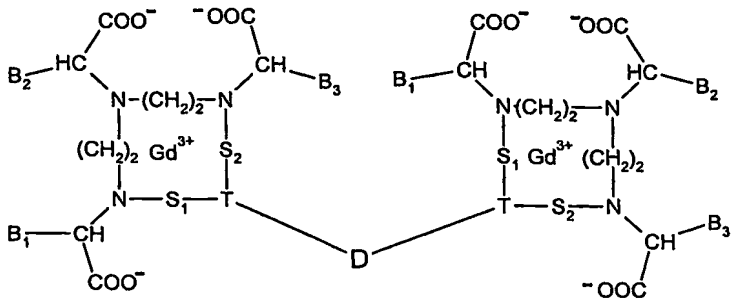
and GNH chosen from :

the groups $-(CH_2)_n-NH-$ with n = 1 to 4,

or  with p = 0 to 3 ;

5. Compound according to Claim 3, characterized in that HR Ch represents a group chosen from :

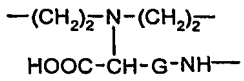
1) the group



II2

in which

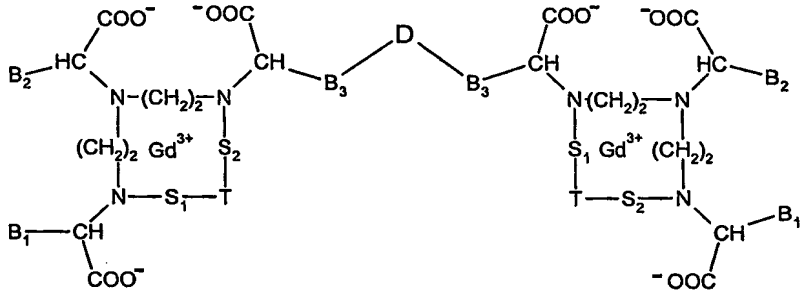
$-S_1-T-S_2-$ is



where $S_1 = S_2 = (CH_2)_2$

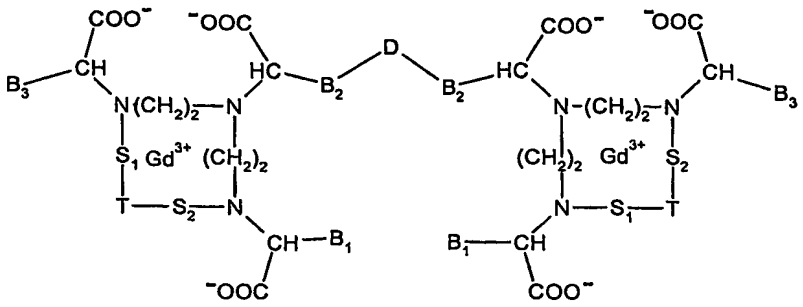
all three of B_1, B_2, B_3 representing $(CH_2)_xCONHR$ with x = 1, 2 or 3

2) the group



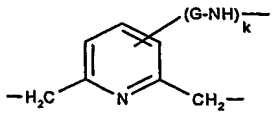
IIa2 (compound referred to as N-functionalized PCTA)

or IIb2 (compound referred to as N-functionalized PCTA and positional isomer of IIb2)



IIb2

in which S_1-T-S_2- is :



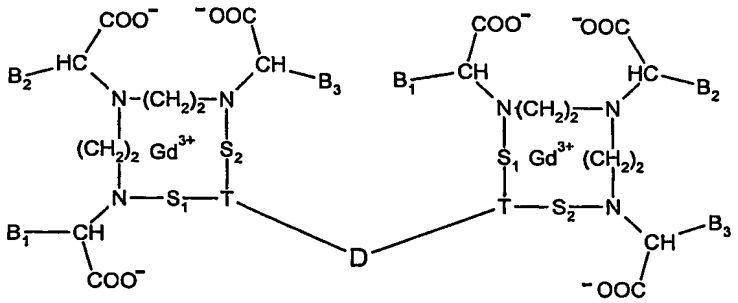
III2

with k = 0 and $S_1 = S_2 = CH_2$;

B_3 representing G-NH, and B1 and B2 representing $(CH_2)_xCONHR$ for IIa2

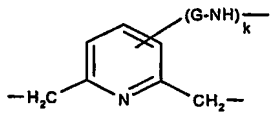
B_2 representing G-NH, and B1 and B3 representing $(CH_2)_xCONHR$ for IIb2

3) the group



IIc2 (compound referred to as C-functionalized PCTA)

when S_1-T-S_2- is :



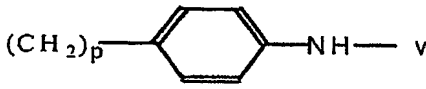
III2

with k = 1 and $S_1 = S_2 = CH_2$;

all three of B_1, B_2, B_3 representing $(CH_2)_xCONHR$ with x = 1, 2 or 3 for IIc2

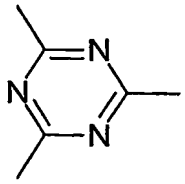
given that, for II2, IIa2, IIb2 and IIc2,

GNH is chosen from the groups $-(CH_2)_n-NH-$ with n = 1 to 4,

or -  with p = 0 to 3 ;

6. Compound according to any one of Claims 1 to 5, characterized in that D is an aromatic backbone polyfunctionalized with carboxylate and/or amino groups, D preferably being of 1,3,5-triazine type, of formula :

linker 2



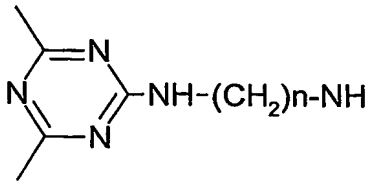
with linker 2 chosen from a) and b) and preferably a) :

a) $(CH_2)_2$ - ϕ - NH_2 , $(CH_2)_3$ - NH_2, NH-$(CH_2)_2$-NH, NH-$(CH_2)_3$-NH,

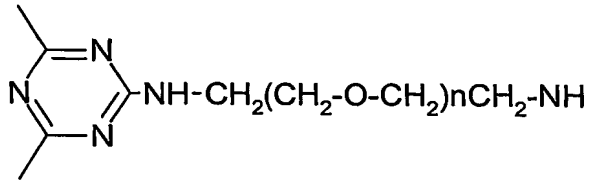
b) P1-I-P2, which may be identical or different, P1 and P2 being chosen from OH, SH, NH_2, nothing, CO_2H, NCS, NCO, SO_3H,

with l = alkylene, alkoxyalkylene, polyalkoxyalkylene, alkylene interrupted with phenylene, alkylidene, alkilidene,

and D being more preferably :



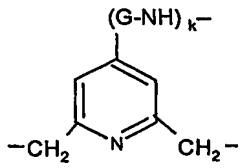
or



7. Compound according to any one of Claims 1 to 6, characterized in that L is a linker chosen from polyoxyalkylenes, squaric acid, a squarate-PEG radical, an alkylene, alkoxyalkylene, polyalkoxyalkylene, alkylene interrupted with phenylene, alkylidene, alkilidene.

8. Compound according to any one of Claims 3 to 7, in which x of $(CH_2)xCONHR$ is 2.

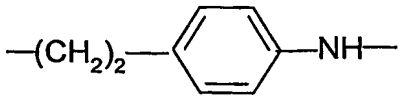
9. Compound according to any one of Claims 4 to 8, in which $-S_1-T-S_2-$ represents:



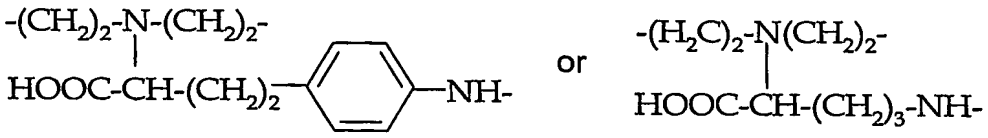
with $S_1 = S_2 = CH_2$.

10. Compounds according to Claim 9 of formula II1 in which k is 1 and G is $-(CH_2)_3-$.

11. Compounds according to Claim 9 of formula II1 in which k is 0 and B_2 or B_3 represents-(-CH_2)$_3$NH- or



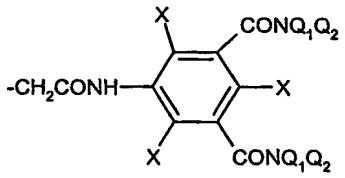
12. Compound according to any one of Claims 4 to 9, in which $-S_1 - T - S_2-$ represents:



with $S_1 = S_2 = (CH_2)_2$.

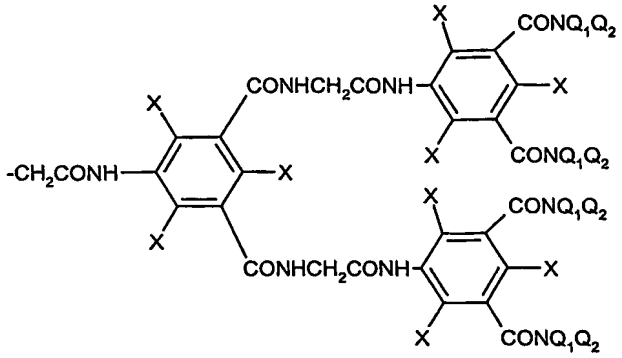
13. Compounds according to any one of the preceding claims, for which B_1, B_2 and B_3, when they do not represent -G-NH, represent -$(CH_2)_2$CONHR, with, in R, p = q = 0 and Z being -CH_2CONH.

14. Compounds according to Claim 13, for which R represents:



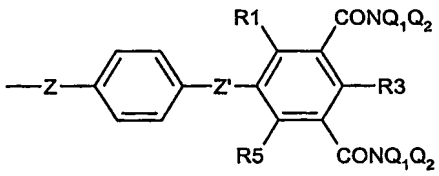
and the X are identical and represent Br or I, while Q_1 and Q_2, which may be identical or different, are mono- or polyhydroxylated (C_1-C_8)alkyl groups such that each $CONQ_1Q_2$ contains from 4 to 10 hydroxyls in total.

15. Compounds according to Claim 13, for which R represents:



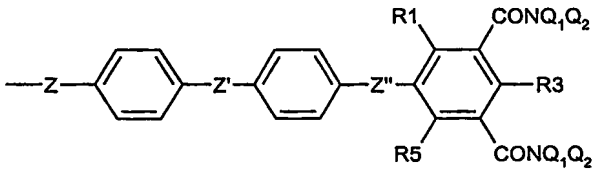
and the X, which are identical, are Br or I, and Q_1 and Q_2, which may be identical or different, are mono- or polyhydroxylated (C_1-C_8)alkyl groups such that each $CONQ_1Q_2$ group contains from 4 to 10 hydroxyls in total.

16. Compounds according to any one of Claims 1 to 12, for which R represents:



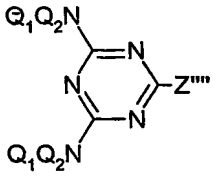
Z is CH_2 or CH_2CONH, Z' is CONH or $CONHCH_2CONH$, R_1, R_3 and R_5, which are identical, are Br or I, and Q_1 and Q_2, which may be identical or different, are mono- or polyhydroxylated (C_1-C_8)alkyl groups such that each $CONQ_1Q_2$ group contains from 4 to 10 hydroxyls in total.

17. Compounds according to any one of Claims 1 to 12, for which R represents:



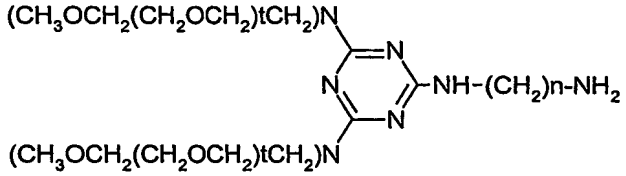
Z is CH_2CONH, Z' is CONH, Z" is $CONHCH_2CONH$ and R_1, R_3 and R_5, which are identical, are Br or I, and Q_1 and Q_2, which may be identical or different, are monohydroxylated or polyhydroxylated (C_1-C_8)alkyl groups such that each $CONQ_1Q_2$ group comprises from 4 to 10 hydroxyls in total.

18. Compounds according to any one of Claims 1 to 12, for which R represents

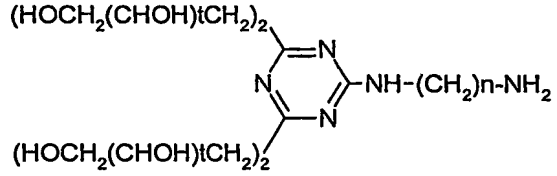


with Z "" being $NQ(CH_2)_j(CH_2OCH_2)_i(CH_2)_jNH_2$, with i = 2 to 6 and j = 1 to 6,

preferably R represents:



or

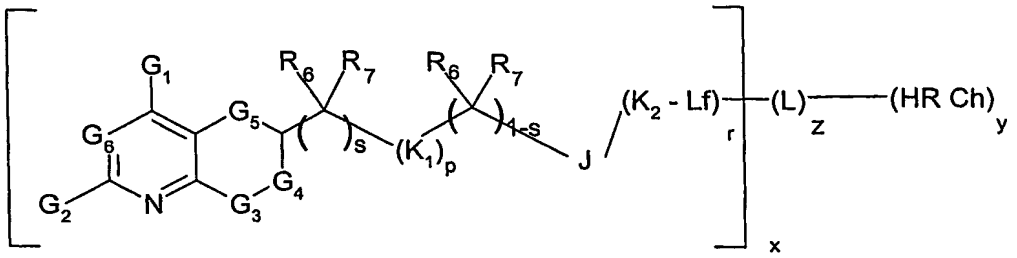


with t =1, 2, 3 or 4 and n=2 to 6.

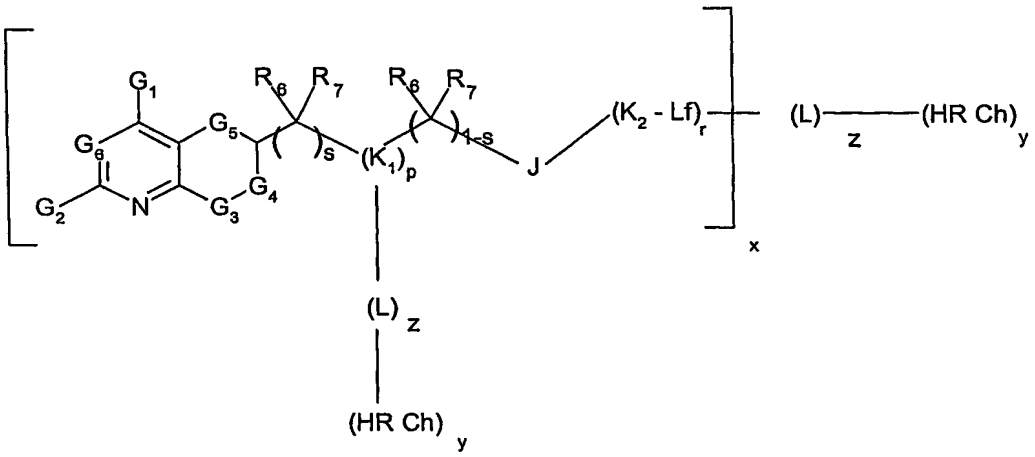
19. Compound according to one of Claims 1 to 18, characterized in that the biovector is an agent capable of targeting cellular receptors or tissue components, in particular chosen from receptors of myocardial cells, of endothelial cells, of epithelial cells, of tumour cells or of immune system cells.

20. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting a folate receptor, (E) being written :

(E1) :



or (E2) :



with :

a) G1 is chosen independently from the group consisting of : halo, R_f2, O R_f2, S R_f3, N R_f4 R_f5 ;

b) G2 is chosen independently from the group consisting of : halo, R_f2, O R_f2, S R_f3, and N R_f4 R_f5 ;

c) G3 and G4 represent divalent groups chosen independently from the group consisting of -(R_f6') C=,-N=,-(R_f6') C (R_f7')-, -N (R_f4')- ;

d) G5 is absent or chosen from -(R_f6') C=,-N=,-(R_f6') C (R_f7')-, -N (R_f4')- ;

e) the ring J is a possibly heterocyclic aromatic 5- or 6-membered ring, it being possible for the atoms of the ring to be C, N, O, S ;

f) G6 is N or C ;

g) K1 and K2 are chosen independently from the group consisting of - C (Z_f)-, -C (Z_f) O, -OC (Z_f)-,-N (R_f4")-,-C (Z_f)-N (R_f4"),-N (R_f4")-C (Z_f),-O-C(Z)-N(R_f4")-, -N(R_f4")-C(Z_f)-O-, N(R_f4")-C(Z_f)-N(R_f5")-, -O-, -S-, -S(O)-, -S$(O)_2$-, -N(R_f4")S$(O)_2$-, -C(R_f6")(R_f7")-, -N(C ≡ CH)-, -N(CH_2-C ≡ CH)-, C_1-C_{12} alkyl and C_1-C_{12} alkoxy; in which Zf is O or S ; preferably K1 is –N(R_f4 ")- or -C(R_f6")(R_f7")- with R_f4", R_f6", R_f7" being H ; K2 possibly being covalently bonded to an amino acid ;

h) R_f1 is chosen from the group consisting of : H, halo, C_1-C_{12} alkyl and C_1-C_{12} alkoxy ; R_f2, R_f3, R_f4, R_f4', R_f 4", R_f 5, R_f5'", R_f6" and R_f7" are chosen independently from the group consisting of : H, halo, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, C,-C, 2 alkanoyl, C,-C, 2 alkenyl, C_1-C_{12} alkynyle, (C_1-C_{12} alkoxy)carbonyl and (C,-C, 2 alkylamino)carbonyl;

i) R_f6 and R_f7 are chosen independently from the group consisting of : H, halo, C_1-C_{12} alkyl, C_1-C_{12} alkoxy; or R_f6 and R_f7 together form O= ;

j) R_f6' and R_f7' are chosen independently from the group consisting of : H, halo, C_1-C_{12} alkyl, C_1-C_{12} alkoxy ; or R_f6' and R_f7' together form O= ;

k) L_f is a divalent linker which includes, where appropriate, a natural amino acid or a natural poly(amino acid), this acid or polyacid being bonded to K2 or to K1 via its alpha-amino group via an amide bond ;

l) n, p, r and s are independently 0 or 1.

21. Compound according to Claim 20, characterized in that G1 is NH_2 or OH.

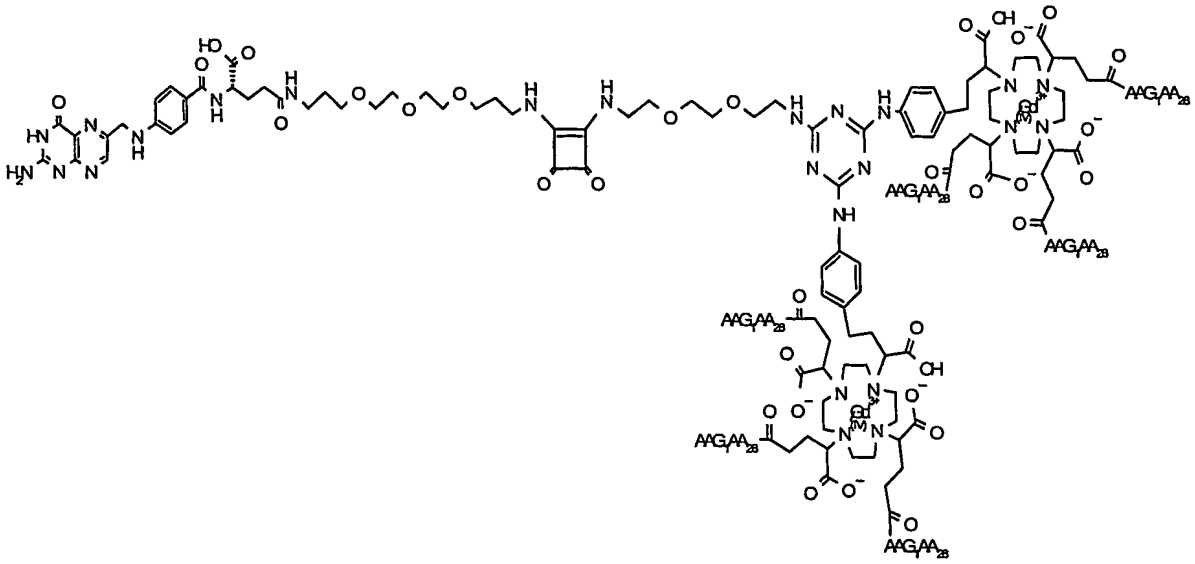
22. Compound according to Claim 20, characterized in that G3 is -N= or –CH- when the ring comprising G3 is aromatic, and G3 is –NH- or -CH_2- when the ring comprising G3 is non-aromatic ; with, preferably, G3 being –CH-, G1 being OH, G6 being NH and K1 being –N(R_f4 ")-.

23. Compound according to Claim 20, characterized in that G4 is –CH- or –$C(CH_3)$-when the ring comprising G3 is aromatic, and –CH_2- or -$CH(CH_3)$- when the ring comprising G3 is non-aromatic.

24. Compound according to Claim 20, characterized in that G5 is absent, with, preferably, G1 being OH, G2 being NH_2, G6 being N.

25. Compound according to Claim 20, characterized in that G6 is N or C.

26. Compound according to Claim 20, characterized in that (E) is



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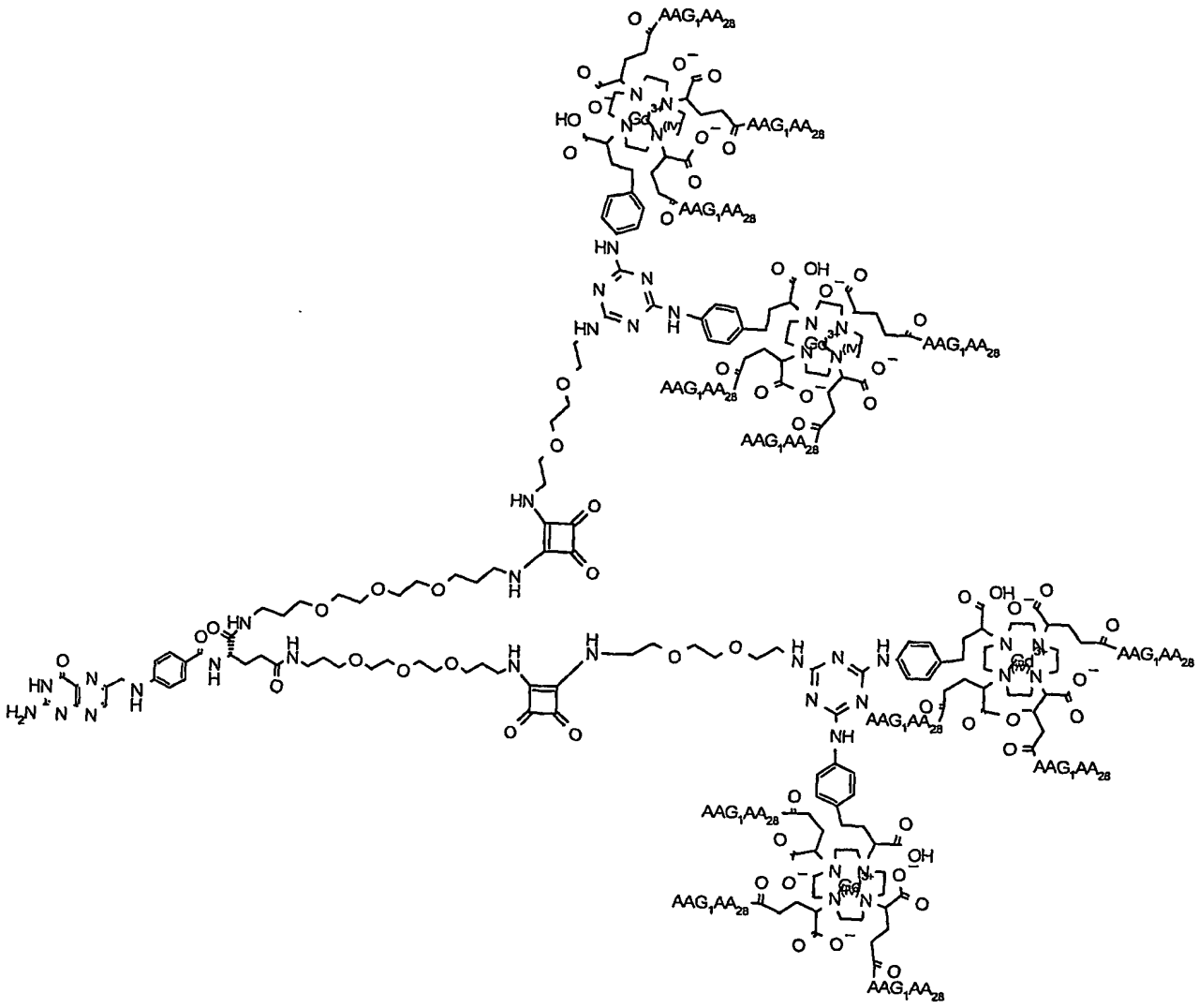


27. Compound according to one of Claims 1 to 19, characterized in that the biovector is an angiogenesis inhibitor.

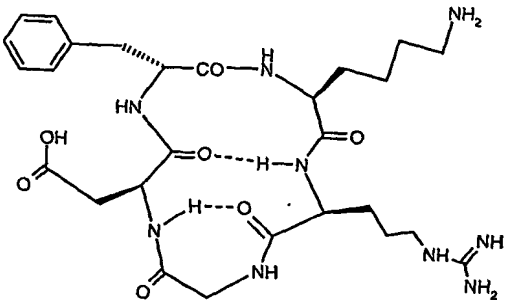
28. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of inhibiting the activity of an MMP.

29. Compound according to Claim 28, characterized in that the biovector is an MMP inhibitor derived from ilomastat .

30. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting an integrin.

31. Compound according to Claim 30, characterized in that the biovector is an agent capable of targeting the integrin αvβ3, in particular an RGD peptide, a peptidomimetic of the RGD peptide, or a non-peptide agent capable of mimicing the action of an RGD peptide.

32. Compound according to Claim 31, characterized in that the biovector is an RGDfV peptide having the structure :



33. Compound according to Claim 30, characterized in that the biovector is an agent capable of targeting the integrin GPIIb/IIIa.

34. Compound according to Claim 30, characterized in that the biovector is an agent capable of targeting a vitronectin.

35. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting an angiogenic receptor of endothelial cells, in particular a VEGFR receptor, preferably a peptide ATWLPPR or HTMYYHHYQHHL.

36. Compound according to one of Claims 1 to 19, characterized in that the biovector is an agent capable of targeting receptors located on macrophages, in particular SRA receptors.

37. Compound according to Claim 36, characterized in that the biovector is a derivative of phosphatidylserine.

38. Compound according to one of Claims 1 to 19, characterized in that the biovector is a bisphosphonate derivative.

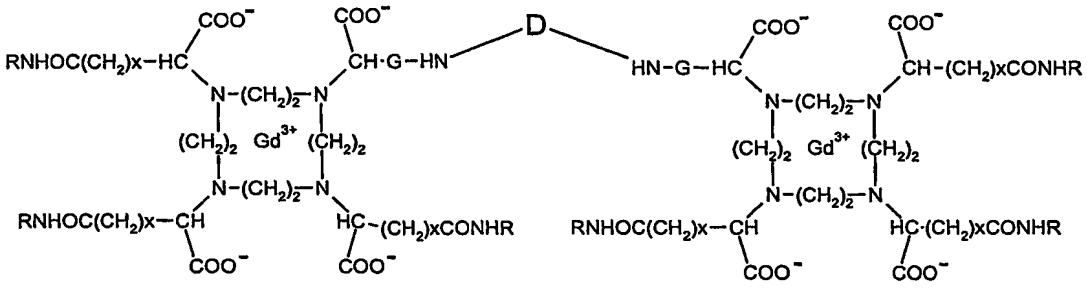
39. Compound according to one of Claims 1 to 19, characterized in that the biovector is a peptide targeting tuftsin.

40. Compound according to one of Claims 1 to 19, characterized in that the biovector is Annexin 5.

41. Intermediate compound, used for preparing a compound according to Claim 1, of formula:

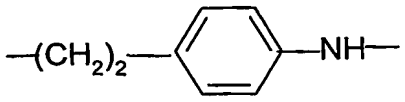
$L - [(D)_q - (I_{a,b,c,d,e,f,g})_r]$

with L preferably of squarate type, q=1 and $[(D)_q-(I_{a,b,c,d,e,f,g})_r]$ preferably being chosen from :

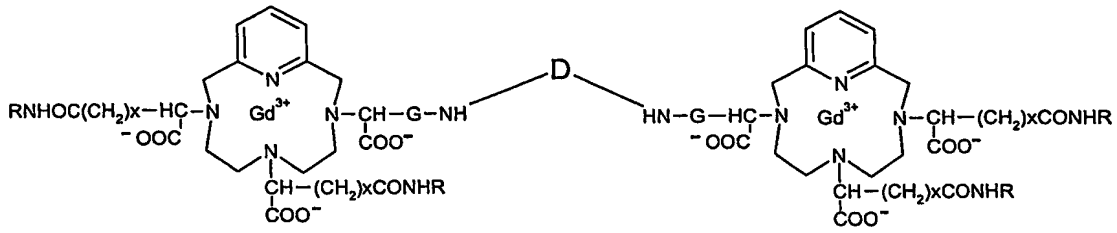


II ' 2

with -G-NH being $-(CH_2)_3-NH-$ or

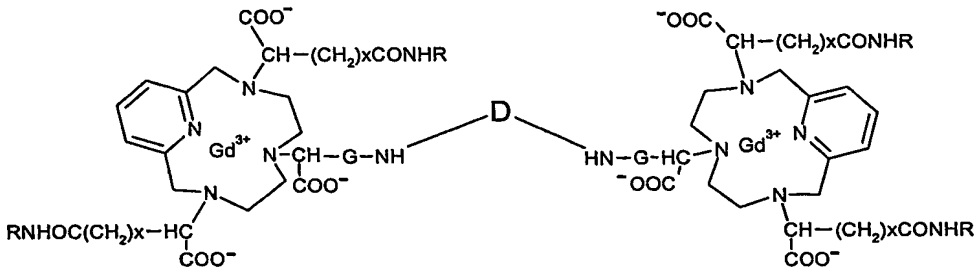


2)

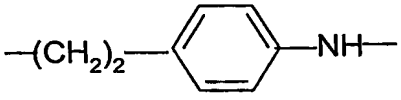


II" a2

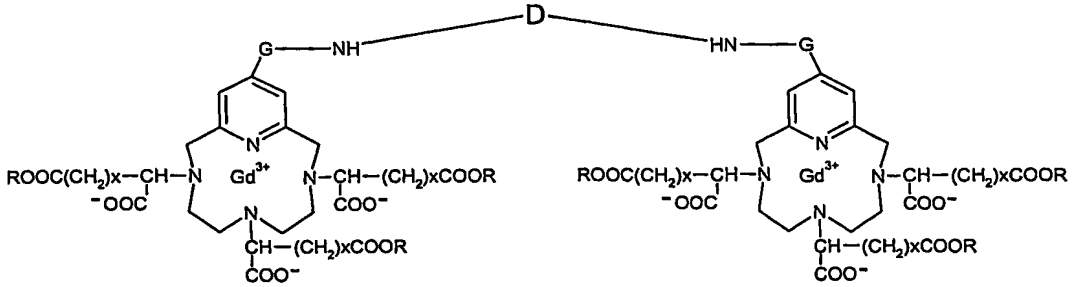
3) II " b2



with -G-NH being $-(CH_2)_3$-NH- or



4)



II ''' 2

with G-NH being -(-CH_2)$_3$-NH-.

42. Compound according to any one of Claims 1 to 40, in its form bonded to an element M, (E) being written $B_x - L - (HR\ Ch)_y - M$; given that M is either a paramagnetic metal ion having the atomic number 21-29, 42-44, or 58-70, or a radionucleide, typically chosen from ^{99}Tc, ^{117}Sn, ^{111}In, ^{97}Ru, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{177}Lu, ^{47}Sc, ^{105}Rh; ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{90}Y, ^{159}Gd, ^{149}Pr, and ^{166}Ho, or a heavy metal ion having the atomic number 21-31, 39-49, 50, 56-80, 82, 83 or 90.

43. Magnetic resonance imaging contrast product, characterized in that it comprises a compound according to one of Claims 1 to 40, optionally combined with a pharmaceutically acceptable vehicle.

44. Contrast product according to Claim 43, provided in the form of an injectable sterile solution.

45. Compound according to either one of Claims 43 and 44, for its use in the diagnosis of a cardiovascular, cancer-related or inflammatory pathology.

46. Nuclear medicine product, characterized in that it comprises a compound according to one of Claims 1 to 38, optionally combined with a pharmaceutically acceptable vehicle.

47. Compound according to any one of Claims 1 to 22, having a relaxivity of between 25 and 200 $mM^{-1}Gd^{-1}$.

48. Method for preparing a compound according to any one of Claims 1 to 40 characterized in that it comprises the coupling of at least one biovector and at least one high-relaxivity chelate as defined in one of Claims 1 to 18.